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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,151	10/30/2001	Jeffrey R. Balser	1242/49/2	8248

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/10/2003

07

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,151	BALSER ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-99* is/are pending in the application.

4a) Of the above claim(s) *4-6 and 20-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-99* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-19, drawn to a method of identifying a compound that modulates a biological activity of a potassium channel in Paper No. 16 (30 July 2003) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-6 and 20-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 16 (30 July 2003).

Claims 1-3 and 7-19 are under consideration in the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. **Specifically, the sequences disclosed in Figure 1A are not accompanied by the required reference to the relevant sequence identifiers. Additionally, the sequences listed in the Paper Copy of 26 July 2002 (Paper No. 10) do not match the sequences in the computer readable format. For example, the Paper Copy lists the total number of sequences as "7" and has SEQ ID NOs: 1-7. However, the CRF only lists the total number of sequences as "5" and has SEQ ID NOs: 1-5.** Applicant must comply with the requirements of the sequence

rules (37 CFR 1.821 - 1.825) in the response to this Office Action in order to be considered responsive.

Specification

1. The disclosure is objected to because of the following informalities:

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example, pg 23, line 16' pg 42, line 18). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF IDENTIFYING A COMPOUND THAT MODULATES THE BIOLOGICAL ACTIVITY OF A HERG/KCR1 COMPLEX".

Appropriate correction is required.

Claim Objections

4. Claim 8 is objected to because of the following informalities: In lines 1-2, the phrase "is comprises a polypeptide" should be amended. Applicant should delete either "is" or "comprises" from the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 and 7-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that increases or decreases the transmission of potassium ions through a human ether-a-go-go-related gene (HERG) potassium channel, comprising: (a) culturing a cell comprising a HERG potassium channel of SEQ ID NO: 3 and a K+ channel regulator 1 (KCR1) polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1; (b) contacting the cell with a test compound; (c) measuring the transmission of potassium ions through the HERG channel in the presence of the test compound; and (d) comparing the potassium ion transmission through the HERG channel in the presence of the test compound to the potassium ion transmission through the HERG channel in the absence of the test compound, wherein a difference in potassium ion transmission through the HERG channel indicates the test compound increases or decreases potassium ion transmission, does not reasonably provide enablement for a method of identifying a compound that modulates a biological activity of a potassium channel comprising, (a) providing a structure comprising a potassium channel polypeptide and a KCR1 polypeptide; (b) contacting the test compound with the structure; (c) determining a biological activity of the potassium channel polypeptide in the presence of the test compound; (d) comparing the biological activity of the potassium channel polypeptide in the presence of the test compound to the biological activity of the potassium channel in an absence of test compound, wherein a difference between the biological activity of the potassium channel in the absence of the test compound and the biological activity of the potassium channel polypeptide in the presence of test compound indicates modulation of a biological activity of the potassium channel. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite that the structure is a cell and that the cell is isolated from a subject. The claims recite that the potassium channel is HERG, which comprises the polypeptide sequence set forth in SEQ ID NO: 3. The claims recite that the KCR1 polypeptide is encoded by the nucleic acid comprising SEQ ID NO: 1. The claims also recite that the determining comprises employing a patch clamp apparatus and that the biological activity of a structure comprising a potassium channel polypeptide and a KCR1 polypeptide in the presence of a test compound is determined in the presence of an MiRP1 polypeptide, which is encoded by a nucleic acid comprising SEQ ID NO: 4.

The specification teaches that CHO-K1 cells are transiently transfected with plasmids containing HERG, KCR1, and MiRP1 (pg 96, linese 9-15) and that voltage clamp protocols are used to measure potassium currents (pg 96, lines 18-34; pg 97, lines 1-5). The specification discloses that the effect of human KCR1 on HERG block by dofetilide, d-sotalol, and quinidine (compounds that inhibit I_{kr}) is studied (pg 97-99). Regarding dofetilide, d-sotalol, and quinidine block, KCR1 coexpression nearly eliminates or reduces the blocking effect (pg 97-98; Figures 2A-2B, 3A-3D). The specification also teaches that currents generated from either HERG alone or HERG plus MiRP1 are completely blocked by dofetilide (pg 100, lines 1-2). Far less current is blocked when HERG is coexpressed with KCR1 and expression of HERG with KCR1 and MiRP1 was intermediate (pg 100, lines 1-16; Figure 5A-5C). However, the specification does not teach identifying compounds that modulate all possible biological activities of all possible potassium channels. The specification does not teach screening for substances capable of

modulation of potassium channel activation using any potassium channels other than HERG (SEQ ID NO: 3) in conjunction with a human KCR1 polypeptide (encoded by the nucleic acid sequence of SEQ ID NO: 1). The specification also does not disclose that all potassium channels are capable of interacting with the KCR1 polypeptide, as required by the claims. Undue experimentation would be required of the skilled artisan to screen all possible potassium channels and their derivatives with all possible compounds for all possible biological activities. Skolnick et al. (Trends in Biotech 18:34-39) states that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, pg 36). Relevant literature reports that that potassium channels constitute the most diverse class of ion channels with respect to kinetic properties, regulation, pharmacology, and structure (pg 1329, col 2; Tables 3-4; Lehmann-Horn et al. Physiol Rev 79 (4): 1317-1372, 1999). Additionally, over 13 subfamilies have been in humans in both excitable and non-excitable cell types (Lehmann-Horn et al., pg 1329, col 2; pg 1330, col 1).

Due to the large quantity of experimentation necessary to screen all possible potassium channels with all possible compounds for all possible biological activities, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the structural and functional diversity of potassium channels, and the breadth of the claims which fail to recite any limitations as to the potassium channel and biological activity to be examined in the assay, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1-3 and 7-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of identifying a compound that modulates a biological activity of a potassium channel comprising, (a) providing a structure comprising a potassium channel polypeptide and a KCR1 polypeptide; (b) contacting the test compound with the structure; (c) determining a biological activity of the potassium channel polypeptide in the presence of the test compound; (d) comparing the biological activity of the potassium channel polypeptide in the presence of the test compound to the biological activity of the potassium channel in an absence of test compound, wherein a difference between the biological activity of the potassium channel in the absence of the test compound and the biological activity of the potassium channel polypeptide in the presence of test compound indicates modulation of a biological activity of the potassium channel.

As discussed above, the specification teaches that CHO-K1 cells are transiently transfected with plasmids containing the HERG potassium channel, KCR1 polypeptide, and MiRP1 (pg 96, linese 9-15) and that voltage clamp protocols are used to measure potassium currents (pg 96, lines 18-34; pg 97, lines 1-5). However, the specification does not teach any specific potassium channels to be utilized in the assay other than the HERG potassium channel as set forth in SEQ ID NO: 3. The description in the specification that all possible potassium

channels could be utilized in the assay is not adequate written description of an entire genus of potassium channels.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the potassium channels of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The potassium channel itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific potassium channel, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-3 and 7-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Regarding claims 1-3 and 7-19, the acronyms "HERG", "KCR1", and "MiRP1" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

11. The phrase "modulates a biological activity" in claims 1-3 and 7-19 is a relative phrase which renders the claims indefinite. The phrase "modulates a biological activity" is not defined by the claim and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, it is not clear what limitations the terms "modulates" and "biological activity" encompass. It is noted that it is inappropriate to read limitations in the specification into the claims.

12. Claims 1-3 and 7-19 recite the limitation "potassium channel polypeptide" in claims 1 and 15. There is insufficient antecedent basis for this limitation in the claims. It is noted that although the claims recite both a "potassium channel" and a "potassium channel polypeptide", "potassium channel" is the first term to be used in claim 1. (Please note that this issue could be overcome by amending the claims to recite "potassium channel".)

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Articles that discuss HERG and HERG function:

Pearlstein et al. J Med Chem. 46(11):2017-2022, 2003.
Taglialatela et al. Biochem Pharmacol. 55(11):1741-1746, 1998.
Zhang S et al. J. Physiol. 548(Pt 3):691-702, 2003.
Roden et al. Ann Rev Physiol 64: 431-475, 2002.
Numaguchi et al. Circ Res. 87(11):1012-1018, 2000.
Abbott et al. Cell. 97(2):175-187, 1999.
Sesti et al. Proc Natl Acad Sci USA 97(19):10613-10618, 2000.
Weerapura et al. J Physiol. 540(Pt 1):15-27, 2002.
Kamiya et al. Mol Pharmacol. 60(2):244-253, 2001.

Discussion of KRC1 and its interaction with rat eag channels:

Hoshi et al. J Biol Chem. 273(36):23080-23085, 1998.
Hoshi et al. Genbank Accession No. RNU78090, direct submission, 04 Sept 1998.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
01 October 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER